

Marked-Up Copies of Amended Paragraphs

a) Paragraph on page 1, starting on line 27 and ending on line 34:

This application is a continuation of and claims priority under 35 U.S.C. § 120 to co-
pending application number 09/874,514, filed June 5, 2001, which application is a continuation
application of and claims priority under 35 U.S.C. § 120 to 08/986,025, filed December 3, 1997,
now U.S. Patent No. 6,242,469, issued June 5, 2001, which claims priority under 35 U.S.C. §
119(e) to [is based on] U.S. Provisional Application Serial Nos. 60/032,282, 60/033,767,
60/047,941, and 60/055,533, filed December 3, 1996, January 14, 1997, May 22, 1997, May 29,
1997, and August 13, 1997, respectively, the contents of which are hereby incorporated by
reference into this application. This invention was made with government support under grants
CA-28824, CA-39821, CA-GM 72231, CA-62948, and AI0-9355 from the National Institutes of
Health, and grant CHE-9504805 from the National Science Foundation. Additionally, the
present invention was supported in part by a fellowship from the United States Army to
Dongfang Meng (DAMD 17-97-1-7146), and thus the government has certain rights in the
invention.

b) Paragraph on page 3, lines 21-22:

[Figure 3A provides] Figures 3(A) and 3(B) provide syntheses of key iodinated intermediates used to prepare hydroxymethylene- and hydroxypropylene-substituted epothilone derivatives.

c) Paragraph on page 3, lines 24-27:

[Figure 3B provides] Figures 3(C) and 3(D) provide methods of preparing hydroxymethylene- and hydroxypropylene-substituted epothilone derivatives, said methods being useful generally to prepare 12,13-*E* epothilones wherein R is methyl, ethyl, n-propyl, and n-hexyl from the corresponding *E*-vinyl iodides.

d) Paragraph on page 3, lines 29-30:

[Figure 3B shows] Figures 3(E) and 3(F) show reactions leading to benzoylated

hydroxymethyl-substituted desoxyepothilone and hydroxymethylene-substituted epothilone (epoxide).

e) Paragraph on page 4, line 9:

[Figure 6 provides] Figures 6(A) and 6(B) provide a scheme of an olefin metathesis route to epothilone A and other analogues.

f) Paragraph on page 4, line 29:

[Figure 14 shows] Figures 14(A) and 14(B) show the preparation of intermediate 4A.

g) Paragraph on page 5, lines 7-8:

[Figure 18 provides] Figures 18(A) and 18(B) provide a synthetic pathway to a protected intermediate for 8-desmethyl deoxyepothilone A.

h) Paragraph on page 5, lines 10-11:

[Figure 19 provides] Figures 19(A), 19(B) and 19(C) provide a synthetic pathway to 8-desmethyl deoxyepothilone A, and structures of *trans*-8-desmethyl-desoxyepothiolone A and a *trans*-iodoolefin intermediate thereto.

i) Paragraph on page 5, lines 13-22:

[Figure 20 shows (top)] Figure 20(A) shows structures of epothilones A and B and 8-desmethylepothilone and [bottom] Figure 20(B) shows a synthetic pathway to intermediate TBS ester 10 used in the preparation of desmethylepothilone A. (a) (*Z*)-Crotyl-B[(-)-Ipc]₂, -78°C, Et₂O, then 3N NaOH, 30% H₂O₂; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂ (74% for two steps, 87% ee); (c) O₃, CH₂Cl₂/MeOH, -78°C, then DMS, (82%); (d) *t*-butyl isobutyrylacetate, NaH, BuLi, 0°C, then 6 (60%, 10:1); (e) Me₄NBH(OAc)₃, -10°C (50%, 10:1 α/β) or NaBH₄, MeOH, THF, 0°C, (88%, 1:1 α/β); (f) TBSOTf, 2,6-lutidine, -40°C, (88%); (g) Dess-Martin periodinane, (90%); (h) Pd(OH)₂, H₂, EtOH (96%); (I) DMSO, oxalyl chloride, CH₂Cl₂, -78°C (78%); (j) Methyl triphenylphosphonium bromide, NaHMDS, THF, 0°C (85%); (k) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt (87%).

j) Paragraph on page 5, line 29:

[Figure 22 shows] Figures 22(A), 22(B) and 22(C) show a synthetic pathway to prepare epothilone analogue **27D**.

k) Paragraph on page 5, line 31:

[Figure 23 shows] Figures 23(A), 23(B) and 23(C) show a synthetic pathway to prepare epothilone analogue **24D**.

l) Paragraph on page 5, line 33:

[Figure 24 shows] Figures 24(A) and 24(B) show a synthetic pathway to prepare epothilone analogue **19D**.

m) Paragraph on page 5, line 35:

[Figure 25 shows] Figures 25(A), 25(B), 25(C) and 25(D) show a synthetic pathway to prepare epothilone analogue **20D**.

n) Paragraph on page 5, line 37:

[Figure 26 shows] Figures 26(A), 26(B), 26(C) and 26(D) show a synthetic pathway to prepare epothilone analogue **22D**.

o) Paragraph on page 6, lines 1-2:

[Figure 27 shows] Figures 27(A), 27(B) and 27(C) show a synthetic pathway to prepare epothilone analogue 12-hydroxy ethyl-epothilone.

p) Paragraph on page 6, lines 4-7:

[Figure 28 shows] Figures 28(A) and 28(B) show the activity of epothilone analogues in a sedimentation test in comparison with DMSO, epothilone A and/or B. Structures 17-20, 22, and 24-27 are shown in Figures 29-37, respectively. Compounds were added to tubulin (1mg/ml) to a concentration of 10 μ M. The quantity of microtubules formed with epothilone A was defined as 100%.

q) Paragraph on page 6, lines 30-32:

[Figure 39 shows] Figures 39(A) and 39(B) show epothilone A and epothilone analogues #1-7. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

r) Paragraph on page 6, lines 34-36:

[Figure 40 shows] Figures 40(A) and 40(B) show epothilone B and epothilone analogues #8-16. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

s) Paragraph on page 7, lines 1-3:

[Figure 41 shows] Figures 41(A) and 41(B) show epothilone analogues #17-25. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

t) Paragraph on page 7, lines 5-7:

[Figure 42(A) shows] Figures 42(A) and 42(B) show epothilone analogues #26-34. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

u) Paragraph on page 7, lines 10-12:

[Figure 42(B) shows] Figures 42(C) and 42(D) show epothilone analogues #35-46. Potencies against human leukemia CCRF-CEM (sensitive) and CCRF-CEM/VBL MDR (resistant) sublines are shown in round and square brackets, respectively.

v) Paragraph on page 7, line 14:

[Figure 42(C) shows] Figure 42(E) shows epothilone analogues #47-49.